Expedited Procedure
Under 37 C.F.R. § 1.116

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of
Manne Satyanarayana Reddy et al. Art Unit: 1625

Application No.: 10/647,449 Examiner: Celia C. Chang

Filed: 25 August 2003

For: POLYMORPHIC FORMS OF (S)-REPAGLINIDE AND THE PROCESSES FOR PREPARATION THEREOF

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Commissioner for Patents
P.O. Box 1450
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Sir:

RESPONSE

This Response is submitted in reply to the Office Action that was mailed on March 6, 2006 for the above-identified patent application, to which a response is due by June 6, 2006. Accordingly, this Response is being timely filed.

Claims 1-2, 4-38, 40-48, 50-51, 53-54, and 56-57 of the subject application are pending. Applicants are not currently amending, canceling, or adding any claims. Accordingly, claims 1-2, 4-38, 40-48, 50-51, 53-54, and 56-57 remain present for further consideration.

In view of the following discussion, applicants respectfully request reconsideration and withdrawal of the final rejections made in the Office Action.

Rejection of Claims 38 and 40-49 under 35 U.S.C § 102(b) as being anticipated by *Grell et al. '924.*

The Examiner has finally rejected claims 38 and 40-49 under 35 U.S.C § 102(b) as being anticipated by United States Patent No. 5,312,924 (*Grell et al. '924*). The Examiner states that *Grell et al. '924* discloses a noncrystalline solid, which is amorphous and is obtained by the same process as claimed by applicants (example 4, col. 23, lines 15-17). The Examiner states that there is only one amorphous product of a given material and that *Ulicky* (Comprehensive Dictionary of Physical Chemistry, p. 21) discloses that solids can be subdivided into crystalline or amorphous forms. The Examiner further states that the Concise Encyclopedia Chemistry (*Eagelson*, pp. 872-873, 1993) defines polymorphs as multiple crystalline forms of compounds and any X-ray diffraction data of an amorphous material is only to show no diffraction or non-crystallinity. The Examiner therefore argues that incorporation of X-ray diffraction data into the base claim does not change the product. Applicants traverse the Examiner's rejections.

Applicants are not able to agree that there can be only a single amorphous form of a given material. No evidence has been cited in support of this proposition, and it seems to not be in accord with the published literature describing amorphous carbon, which is known to include materials having differing properties. See, for example, the article by B. Gopalakrishnan et al., "Many Phases of Carbon," *Resonance*, Dec. 2002, pages 10-19, which discusses several different amorphous carbons at pages 17-19. A copy of the article is enclosed.

Applicants' claim 38 recites a "compound which is an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4.

Applicants' claim 40 recites a "process for making an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4, said process comprising: (a) providing a solution of (S)-repaglinide in a C_1-C_4 alcohol; (b) cooling said solution so that a solid mass separates; and (c) isolating said separated

solid mass to provide the amorphous form of (S)-repaglinide. Claims 41-49 are dependent from claim 40.

Ulicky states that:

> Some authors also sub-divide solids into crystalline and amorphous. As amorphous they, consider those which are rigid and keep their shape but which do not exhibit a crystal structure (glasses, metallic glasses, resins, some plastic substances). According to other authors, such substances should be regarded as supercooled liquids with very high viscosities (> 10^{13} Pas).
>
> This ambiguity follows from insufficient knowledge, about the structure of non-crystalline solids. *Ulicky* at p. 21. (emphasis added)

Moreover, applicants submit that *Grell et al. '924* does not teach applicants' process for making an amorphous form of (S)-repaglinide as recited in claim 40. *Grell et al. '924* discloses in Example 4 the crystallization of (S)-repaglinide from petroleum ether by the addition of ethanol. Applicants' amorphous form of (S)-repaglinide is prepared by providing a solution of (S)-repaglinide in a C_1-C_4 alcohol and cooling the solution to provide the amorphous form of (S)-repaglinide. *Grell et al. '924* also does not disclose an amorphous form of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4. In summary, *Grell et al. '924* does not teach each and every element of applicants' amorphous form of (S)-repaglinide. Accordingly, *Grell et al. '924* does not anticipate applicants' claims under 35 U.S.C. § 102(b).

Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art. *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added). We think the precise language of 35 U.S.C. §102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a

burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under §102 and §103. *In re Warner*, 154 USPQ 173, 177 (C.C.P.A. 1967), cert. denied, 389 U.S. 1057 (1968).

Hence, the Examiner's rejection of claims 38 and 40-49 under 35 U.S.C § 102(b) as being anticipated by *Grell et al.'924* should be withdrawn.

Rejection of Claims 1 and 34-35 under 35 U.S.C §102 (b) as being anticipated by *Grell et al. '924.*

The Examiner has rejected claims 1 and 34-35 under 35 U.S.C §102(b) as being anticipated by *Grell et al. '924*. The Examiner states that *Grell et al. '924* (col. 23) discloses crystallized compounds of the present claims. The Examiner argues that a novel or unobvious chemical product is identified by its chemical nature (i.e., its elemental content and their ratios) and that many pharmaceutical solids exhibit polymorphism, which is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. The Examiner concludes that the term "Form III" does not offer any demarcation of the product from the prior art crystalline product as represented by the compound name since Form III or Form A, B, or C in the prior art are not notations known in the chemical art to represent conventional characteristics in demarcating chemical products.

The Examiner states that the finding of anticipation is whether the claims and the prior art are "same identical" product not what physical parameters (X-ray diffraction pattern data) are used in claiming them. The Examiner argues that to extend the identifier being IR, the instant product and the prior art products are essentially the same (see Figure 4 and combined part I and II of Figures 2-3 of *Grell et al. '924)*. The Examiner states that no evidence in the record shows that the instant crystalline form and the prior art A, B, or C are different especially when the IR are essentially the same and although 2 theta values and d-spacing are useful in identifying different crystalline forms, margin of error existed (page 16 of applicants' specification). Therefore, the

Examiner concludes that single 2 theta patterns do not demarcate the product from another without multiple identifiers which when compared two forms clearly can demarcate each to be different products given the margin of error. Applicants traverse the Examiner's rejection.

Claim 1 recites a "compound, which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1." Claims 34-35 depend from claim 19. Claim 19 recites a "process for preparing a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1, said process comprising: (a) providing a solution of (S)-repaglinide in a haloalkane solvent; (b) contacting said solution with a C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent thereby forming a precipitate; and (c) isolating the precipitate to provide the crystalline Form III of (S)-repaglinide."

Claims 1 and 34-35 do not recite infrared spectra data or 2 theta values but rather recite X-ray powder diffraction patterns.

Applicants submit that *Grell et al. '924* does not anticipate applicants' claims. *Grell et al. '924* discloses crystallization of (S)-repaglinide from petroleum ether by the addition of ethanol. Applicants' crystalline Form III of (S)-repaglinide is prepared by providing a solution of (S)-repaglinide in a haloalkane solvent and contacting the solution with a C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent thereby forming a precipitate and providing the crystalline Form III of (S)-repaglinide. *Grell et al. '924* also does not disclose a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1. In summary, *Grell et al. '924* does not teach each and every element of applicants' crystalline Form III of (S)-repaglinide. Accordingly, *Grell et al. '924* does not anticipate applicants' claims under 35 U.S.C. § 102(b).

Polymorphs arise when molecules of a compound arrange in the solid state in distinct ways. By varying the temperature of the solution and using different solvents, different polymorphs can be formed. Although identical in chemical composition, polymorphs can have very different properties. Polymorphs are distinguishable by various analytical techniques, especially X-ray powder diffraction patterns.

Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art. *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added). We think the precise language of 35 U.S.C. §102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under §102 and §103. *In re Warner*, 154 USPQ 173, 177 (C.C.P.A. 1967), cert. denied, 389 U.S. 1057 (1968).

Hence, the Examiner's rejection of claims 1 and 34-35 under 35 U.S.C §102 (b) as being anticipated by *Grell et al. '924* should be withdrawn.

Rejection of Claims 1-37, 39, and 50-57 under 35 U.S.C. § 103(a) as being unpatentable over *Grell et al. '924,* in view of *Grell et al. J. Med. Chem.*, and *Brittain*.

The Examiner has rejected claims 1-37, 39, and 50-57 under 35 U.S.C. § 103(a) as being unpatentable over *Grell et al. '924* in view of J. Med. Chem. **1998**, *41*, 5219-5246 (*Grell et al. J. Med. Chem.*) and Polymorphism in Pharmaceutical Solids, edited by Harry G. Brittain, Marcel Dekker 1999 (*Brittain*). The Examiner states that *Grell et al. '942* discloses compounds that anticipate the base claims as pointed out above. The Examiner concedes that *Grell et al. '942* does not disclose the physical properties of the prior art products or the method of making the products employing alternative solvents. The Examiner argues that *Grell et al. J. Med. Chem.* discloses making different crystalline forms using various solvents (page 5227, paragraph below Table 2). The

Examiner further argues that *Brittain* discloses that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or conformations of the molecules."

The Examiner states that the claims are *prima facie* obvious because the instant claims differ from the known products merely by forms and the physical properties innate to the forms. The Examiner argues that there is nothing unobvious about the innate nature of a drug because it is recognized that the innately existed different "morph" will display different physical properties such as X-ray diffraction pattern, melting point, etc. (*Brittian* at p. 178-179, 219). The Examiner contends that for a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, purification, preparation or synthesis, hydroscopicity, recovery, or prevention of precipitation. The Examiner argues that *Grell et al. J. Med. Chem.* (p. 5227) discloses using different solvents in the crystallization process. The Examiner concludes that in the absence of unexpected results, the use of such different solvents may produce products with different physical properties, which are innate to the product.

The Examiner states that even if the X-ray diffraction pattern of the present invention is different from the product of the prior art, it is "in the strictest sense, the same pure substance " of the prior art, i.e., prima facie obvious unless some form of unobviousness can be provided (Brittain p.185). The Examiner contends that a mere difference in physical parameters, such as X-ray diffraction pattern, does not offer any unexpected advantage of prior art product with the same chemical property and biological property, i.e., a mere variation in physical forms. Applicants traverse the Examiner's rejection.

Applicants' claim 50 recites a "process for preparing a crystalline Form II of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Table 3, said process comprising: (a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether; (b) cooling said solution thereby separating a solid mass; and (c) isolating said

solid mass to provide the crystalline Form II of (S)-repaglinide." Claims 51-57 are dependent from claim 50.

The Examiner concedes that *Grell et al. 942* does not disclose the physical properties of (S)-repaglinide or the method of making the products employing alternative solvents.

The *Grell et al. J. Med. Chem.* reference discloses the structure-activity relationships of two series of hypoglycemic benzoic acid derivatives. Table 2 in *Grell et al. J. Med. Chem.* discloses the substituted benzoic acid derivatives prepared and their respective pharmacological activities. *Grell et al. J. Med. Chem.* does not disclose any polymorphs of (S)-repaglinide and does not disclose any of applicants' processes for preparing polymorphs of (S)-repaglinide

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 706.02(j)

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). MPEP 706.02(j).

The art recognizes the importance of identifying all possible polymorphic forms of a drug substance, and the difficulties encountered in doing so. See, for example, A. Goho, "Tricky Business," *Science News,* Vol. 166, No. 8, pages 122-123 (August 21,

2004), an eight-page website reprint of the article having previously been provided by applicants. The U.S. Food and Drug Administration published a draft guidance document in December 2004 relating to polymorphism, recommending that ANDA applicants for marketing approval investigate whether their drug substance can exist in polymorphic forms, including crystalline forms, amorphous forms, and solvates.

Applicants submit that this rejection is entirely analagous to the rejection of claims for amorphous raloxifene that was made in Application No. 08/918,741 (now U.S. Patent 6,713,494). Those rejections of claims to the amorphous raloxifene were discussed by the Board of Patent Appeals and Interferences in the decision for Appeal No. 2001-2157, and were reversed because obviousness requires that the prior art must lead a person having ordinary skill in the art to the claimed invention with a reasonable likelihood of success.

Further, the rejection is analogous to the obviousness rejection of claims to various crystalline forms of a previously known compound in Application No. 09/166,445 (now U.S. Patent 6,713,481). The Board of Patent Appeals and Interferences reversed those rejections in Appeal No. 2002-0941, stating that there is no *per se* rule that changing the form, purity, or another characteristic of an old product does not render the claimed product patentable.

Hence, the Examiner's rejection of claims 1-37, 39, and 50-57 under 35 U.S.C. §103(a) as being unpatentable over *Grell et al. 924* in view of *Grell et al. J. Med. Chem.* and *Brittain* should be withdrawn.

Rejection of Claims 8-18 under 35 U.S.C. §112, first paragraph.

The Examiner has rejected claims 8-18 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that it is well known in the pharmaceutical formulation field that polymorphs may undergo transformation when being formulated into compositions (*Rouhi*, Chem. Eng. News, 24 February 2003, pp. 34-35). The Examiner argues that in absence of any description or factual evidence, the specification lacks description and enablement that the

pharmaceutical composition contains the claimed "form" without transformation and there is no basis in the specification to support the transformation of less than 1-5% as found in claims 9-14.

The Examiner states that transformation of the Form III to other forms indicates the metastable nature of Form III and the article by A. Goho provided by applicants clearly states that composition maintaining the particular form is far from routine but may cost millions of dollars and effort to obtain (see p. 2, "Disappearing Act"). The Examiner concludes that absent any description that the particular form or X-ray can be obtained in a "composition", the deficiency of description as compared to the art standard described in the article "Tricky Business", is self-evident. Applicants traverse the Examiner's rejections.

Applicants' independent claim 8 provides a composition comprising (S)-repaglinide as a solid, wherein at least 80% by weight of said solid (S)-repaglinide is in crystalline Form III, which has an X-ray powder diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.44 ± 0.09, 6.81 ± 0.09, 7.80 ± 0.09, 9.28 ± 0.09, 11.09 ± 0.09, 11.89 ± 0.09, 12.92 ± 0.09, 13.46 ± 0.09, 14.34 ± 0.09, 15.77 ± 0.09, 16.24 ± 0.09, 17.08 ± 0.09, 18.06 ± 0.09, 18.75 ± 0.09, 19.25 ± 0.09, 19.59 ± 0.09, 19.99 ± 0.09, 20.34 ± 0.09, 21.18 ± 0.09, 21.96 ± 0.09, 22.18 ± 0.09, 22.58 ± 0.09, 23.24 ± 0.09, 23.77 ± 0.09, 24.08 ± 0.09, 25.02 ± 0.09, 25.31 ± 0.09, 25.78 ± 0.09, 26.67 ± 0.09, 27.39 ± 0.09, 28.03 ± 0.09, 30.26 ± 0.09, 35.50 ± 0.09, and 38.74 ± 0.09 degrees.

Applicants' independent claim 15 provides a pharmaceutical composition formed by combining: a) a compound which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1; and b) a pharmaceutically acceptable carrier or diluent.

The *Rouhi* reference discloses that polymorphs may undergo transformation when being formulated into pharmaceutical compositions but *Rouhi* also discloses that polymorphism and crystallization may be mastered from start to finish (*Rouhi* at p. 34). The Examiner's position that applicants' polymorphs may undergo transformation when

being formulated into compositions is only unsupported speculation, which cannot properly serve as the basis for a rejection.

Applicants' specification needs to describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it. When an invention involves distinct arts, that specification is adequate which enables the adepts of each art, those who have the best chance of being enabled, to carry out the aspect proper to their specialty.

> The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.,* 221 USPQ 481, 489 (Fed. Cir. 1984)
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> It has been consistently held that the first paragraph of 35 U.S.C. §112 required nothing more than objective enablement... In satisfying the enablement requirement, as application need not teach, and preferably omits that which is well-known in the art.....How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. .
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> The error we see in *Staehelin's* approach to the question before us is that *Staehelin* would require a patent specification to be a blueprint, which, if followed, would unfailingly reproduce exactly an applicant's claimed invention. However, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. §112, first paragraph. *Staehelin v. Secher,* 24 USPQ2d 1513, 1516 (B.P.A.I. 1992)

Applicants submit that one having ordinary skill in the art will be able to determine whether a particular composition falls within the scope of the applicants' claims. If transformation has occurred and a claim limitation is not being met, then that fact will be readily apparent. There can be no issue of a lack of enablement.

Hence, the Examiner's rejection of claims 8-18 under 35 U.S.C. §112, first paragraph, should be withdrawn.

CONCLUSION

In view of the foregoing remarks, applicants request reconsideration pursuant to 37 C.F.R. § 112 and allowance of all of the claims pending in this application. Applicants suggest that the Examiner telephone the undersigned attorney should the Examiner have any questions or comments, which might be most expeditiously handled by a telephone conference or personal interview.

No fee is deemed necessary in connection with the filing of this Response. If any fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 50-3221.

Respectfully submitted,

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